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Reply to: "ALPPS procedure for hepatocellular carcinoma with macrovascular thrombosis: A new opportunity?"

To the Editor:

We would like to thank Levi Sandri and colleagues for their comments regarding our recently published article [1]. The authors support our result that neither tumour thrombosis in a major hepatic vein (mHVTT) nor portal vein tumour thrombosis, not invading the main portal trunk, is a contraindication for liver resection. In addition, they proposed further an aggressive strategy for unresectable hepatocellular carcinoma (HCC), i.e., associating liver partition and portal vein ligation in a staged hepatectomy (ALPPS) [2].

HCC with macroscopic vascular invasion is a challenging situation for surgical resection [3], and major hepatic resection is often required [1,4,5]. Considering the progressive nature of the disease, an urgent operation is also required. These situations complicate the decision-making process, and many cases miss their chance for a curative resection. Since ALPPS is reportedly associated with a rapid hypertrophy of the remnant liver [2], this technique may be a promising strategy for treating HCC with macroscopic vascular invasion.

We have never attempted ALLPS in this setting. Instead, we have proposed preoperative portal vein embolization (PVE) as a possible strategy in cases with an insufficient postoperative remnant liver volume [6]. Actually, among 14 patients who underwent a major hepatic resection for mHVTT, 4 patients (29%) underwent preoperative PVE [1]. At present, PVE may be a standard strategy with an acceptable morbidity rate [7].

The presence of portal hypertension and impaired liver function (a 15 min indocyanine green retention rate of more than 20%) are contraindications for PVE [8]. These safety restrictions should also be applied to ALPPS, since it is a more aggressive strategy. As Levi Sandri *et al.* proposed, the Child-Pugh score and the model for end-stage liver disease score may be useful for making treatment-related decisions.

Data on this attractive approach are now being accumulated through a worldwide registry system. However, the available evidence remains insufficient to support the use of ALPPS in cirrhotic patients with HCC [2,9]. Most of the evidence regarding ALPPS is based on patients with colorectal liver metastases, in whom the liver function has not been severely damaged. We expect further reports on the role of the ALPPS procedure for HCC patients requiring major hepatectomy.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Chronic kidney disease after liver transplantation

To the Editor:

We read with interest the report by Allen *et al.* in a recent issue of the *Journal of Hepatology* [1]. The authors are to be congratulated on highlighting the important problem of chronic kidney disease (CKD) in liver transplant recipients. Instead of concentrating on severe CKD (KDIGO stages 4–5) as in most previous literature, their study additionally describes the incidence of lesser degrees of renal injury (KDIGO stage 3) and has the benefit of an iothalamate-measured glomerular filtration rate (GFR). They found that few patients maintained 'normal' renal function long-term after

transplantation, with two thirds developing CKD by 10 years. The majority of patients had stage 3 disease. However, echoing observations in the non-transplant setting, this moderate CKD (GFR <60 ml/min/1.73 m^2) was clinically relevant having implications for survival [2,3].

There are several points worthy of comment. First, although there was clearly a progressive deterioration in renal function with time after transplant, the greatest loss occurred within the first year. The authors speculate that this reflects nephrotoxic immunosuppressive drugs. Little mention was made of the role of peri-operative acute kidney injury (AKI). In our unit, despite optimized pre-transplant renal function and less calcineurin inhibitor exposure in recent years, patients are experiencing more GFR loss from baseline to 1-year [4]. This is in the context of a rise in the incidence of AKI that has occurred in parallel with a marked rise in the use of higher risk grafts [4]. We have hypothesized that graft injury may play a critical role in the pathogenesis of AKI in this setting. It is well recognized that AKI can cause permanent structural damage, with progressive tubulo-interstitial fibrosis and long-term repercussions for renal function [5]. Therefore, we suggest that in addition to renal sparing immunosuppression, future strategies to prevent CKD may include therapies that minimize the renal hit at time of transplantation.

Second, the apparent lack of era effect on the frequency of CKD is interesting. United States registry data has shown that the introduction of MELD has been accompanied by an increased likelihood of end-stage kidney disease, which has been attributed to greater pre-operative renal dysfunction [6]. Nevertheless, given that the adjusted hazard ratio for renal failure only rose by 15% after MELD implementation, one might not anticipate a demonstrable difference in this comparatively small study. Without detailed information, regarding additional recipient and donor factors, it is difficult to draw any real conclusions regarding the evolving incidence of CKD. Readers should not be falsely reassured by this data, especially in the face of an escalating use of higher risk grafts.

Finally, a major conclusion of the study by Allen *et al.* was the limited reliability of creatinine-based GFR estimation in predicting mortality in these patients, and that preventative and expectant management, based on the early recognition of renal dysfunction, may require actual measurement of GFR. We argue that measured GFR is time-consuming, costly and not an applicable test for most transplant centres when repeated tests are necessary. Although a useful research tool, a single absolute measure of renal function in an individual patient is less relevant than delta estimated GFR for modifying clinical care.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Reply to: "Chronic kidney disease after liver transplantation"

To the Editor:

We appreciate the insightful comments of Leithead and Ferguson regarding our recent analysis of prevalence of chronic kidney disease (CKD) after liver transplantation (LT). We agree that peri-operative acute kidney injury (AKI) contributes to the development of chronic kidney disease after LT in a proportion of patients. We did not ascertain the trajectory of renal function in the early postoperative period in all our subjects. Since the first iothalamate clearance measurement was performed at 4 months post-transplantation, we chose this interval as the first point in our time-dependent analysis. Our assumption that in the majority of cases the renal dysfunction is attributed to calcineurin-inhibitor nephrotoxicity was derived from the detailed chart review of a small subset of patients with normal renal function at the time of LT who developed CKD at 4 months. In this random sample, only 27% of patients had postoperative AKI, defined as increase in creatinine by 0.3 mg/dl from baseline [1]. Thus, while we acknowledge that postoperative AKI contributes to post-LT CKD, we cannot quantify the degree to which it contributes to CKD based on our data. We wholeheartedly agree that, given